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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/977,787	11/25/1997	LEE MIZZEN	STS96-02A	3496

26161 7590 03/13/2006

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EXAMINER	
ZEMAN, MARY K	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 03/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/977,787	MIZZEN ET AL.	
	Examiner	Art Unit	
	Mary K. Zeman	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54,57-59,61-69,88-93 and 95-135* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54,57-59,61-69,88-93 and 95-135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 54, 57-59, 61-69, 88-93, and 95-135 are pending in this application. Applicant's amendments and arguments filed 12/21/05 have been carefully considered, but are not persuasive.

The IDS filed 12/27/05 has been entered and considered.

Claims 54, 57-59, 61-69, 88-93, and 95-135 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To the extent this is newly applied, it is necessitated by Applicant's amendments.

The arguments and amendments have been carefully reviewed. The specification and priority documents have been carefully reviewed. Applicant has amended some claims to recite particular stress proteins and/or antigens, or combinations thereof. While each of the names of the proteins are listed in the specification, the mere listing by name is not an enabling disclosure for the currently pending claims.

The specification, as originally filed, fails to provide an enabling disclosure for fusion proteins wherein the protein comprises an antigen (or unidentified portion thereof) of an influenza virus and a stress protein (or unidentified portion thereof) wherein the stress proteins (or portions) are selected from the list in claim 54. The specification only provides information for the stress proteins as names. No specific sequences are identified that the names refer to. No well known references regarding a sequence or stress protein are specifically incorporated by reference. Some papers are cited at page 28 of the specification, however, they are not properly incorporated by reference, and still would not necessarily provide an enabling disclosure. One of skill in the art would require specific sequence information to make and use the invention of the claims. To make a fusion protein which provokes an antigen response as required, one must combine two genes encoding some portion of the influenze proteins and some portion of the stress protein. In the specification, (pages 22-23) it is made clear that the stress proteins named therein have a wide diversity of sequence. The protein known as "hsp70" alone is said to have

more than 10 different specific protein sequences. Hsp90 at least 2. The recitation of the hsp name is not a specific indication of what sequences are to be used in the invention. Without such specific information, it would require undue experimentation for one of ordinary skill in the art to identify which sequences to use, and which portions of those sequences to use, in order to make a protein which falls within the limits of the claims.

Further, methods of using these peptides are not enabled, as one cannot use what one cannot make. (claim 64 drawn to methods of inducing an immune response, etc.)

As set forth previously, factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 (CAFC 1988). The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

The Board has also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below which leads to the determination that the above claims lack enablement due to undue experimentation being required to make and use the invention.

The MPEP at 2164.04 requires that it is necessary to firstly construe the claims before any analysis of enablement can occur. Thusly the above rejected claims have construed to be directed to a polypeptide of an antigen of an influenza virus (or an unidentified antigenic portion thereof) and a stress protein (or an unidentified portion thereof), or the following variants: a polypeptide comprising at least an immunogenic portion, of each part such that the ability of the variant to induce a specific immune response is not substantially diminished. This polypeptide is construed as being prepared via host cell culturing wherein the host cell contains a vector which in turn contains a polynucleotide made up of normally found nucleotides which encode the polypeptide recited above via the translation of normally occurring triplet codons therein into

said polypeptide. See claim 58 wherein the peptide is encoded by a particular plasmid. Methods of using the claimed peptides to induce immune responses are also claimed.

(1) – the quantity of experimentation necessary-

There are an enormous number of polynucleotides, vectors, and host cells to be experimentally tested in order to make a useful polypeptide of a fusion protein comprising one of 7 influenza proteins (or unidentified portions thereof) in fusion with the at least 17 named stress proteins (or unidentified portions thereof) for claim 54, and in fusion with the unnamed stress proteins (or portions thereof) in claim 61. There are no specific sequences set forth in the specification for any of the portions of any of the parts of the claimed peptides. No nucleic acid sequences which encode the proteins are disclosed. Methods of preparing two specific vectors are disclosed, and claims directed specifically to these embodiments may be enabled. Therefore, one of skill in the art would be required to identify desirable sequences for the influenza protein, identify desirable sequences for a stress protein, determine what portions of those proteins to use and then generate polynucleotides encoding them. Regarding the polynucleotides to be tested, the art recognizes that for each amino acid in the claimed fusion proteins that there are degenerate codons available as shown in the well known Biochemistry textbook by Lehninger as in Table 31-5 on page 718. Counting the number of codons results in observing that 5 of the normal amino acids may each be encoded by one of 4 three nucleotide codon options. For 9 of the normal amino acids, 2 such three nucleotide codon options are available. For 3 amino acids, 6 such codon options are available. For 1 amino acid, 3 such codons are utilized. For 2 amino acids, only one such codon is available. An average of the number of codons per amino acid may be approximated via an averaging of the above codon usage as being three available codons for an average amino acid. Without specifying the length of a sequence encoding the claimed fusion proteins, it may be reasonably approximated that it is a polypeptide which falls within the range of polypeptides with sizes as shown in the well known Biochemistry textbook by Lehninger as in Table 3-2 on page 57. A median polypeptide contains 550-800 amino acids. Choosing conservatively, a median polypeptide thus contains 500+ amino acids. Therefore, an estimate of the number of potential polynucleotides encoding the claimed proteins of 500 amino acids would be that calculated at 3 raised to the 500^{th} power. This further calculates to approximately 10^{240} possible polynucleotides to evaluate or experimentally test to find those

useable in making a useful fusion polypeptide, or a polypeptide meeting the limits of the genus of polypeptides in claims 54. Thus, there is an enormous number of polynucleotides to experimentally test to find any that encode the claimed fusions or its variants which are useful. Another experimentation requirement regarded to enable the use of the instantly claimed methods is the determination of a useful activity for the claimed fusion polypeptides. The file history indicates that a specific fusion polypeptides comprising specific stress proteins with specific influenza antigens is useful in provoking an immune response against the influenza antigen. Antigenicity, or the ability to provoke a specific immune response is strongly dependent on the three dimensional structure of the polypeptide. In the well known Biochemistry textbook by Lehninger at pages 58-62, not only is the vast diversity of protein polypeptides set forth regarding functionality, such as enzymatic function, but that each protein has a characteristic three-dimensional shape referred to as its conformation. The specification and claims have not disclosed what **portions** of the parts of the fusion protein are required for antigenicity, and to test for this factor alone relegates the experimentation to undue experimentation regarding a lack of any indication of what experimental test or assay is to be performed. This experimental search for a test is further complicated by a lack of any guidance regarding what single, or even a subset of polynucleotides out of the 10^{240} should be tested. These considerations are supportive of a determination of undue experimentation to find a starting material polynucleotide to be placed in a vector and in turn a host cell for culturing, for production of a polypeptide to be used as claimed.

Turning to the question of what host cell is to be utilized in producing the polypeptide, it is well known that a myriad of thousands of cell types are known to Biotechnology. It is acknowledged that some of these known cell types are more commonly utilized for host cell culturing as described in the specification. Even such commonly utilized host cells number into the hundreds. In USP 5,082,767, Hatfield et al., the expression of polynucleotides in host cells of various types is described in column 1 lines 1-49. Even though such expression practices are frequently carried out, Hatfield et al describe another major problem in this area in column 1 lines 50-65, wherein a protein (or polypeptide) is produced in recoverable quantities, but is inactive. As discussed above, some type of activity (antigenicity) is required for the polypeptide of the claims. A solution is described in Hatfield et al in column 1 lines 61-65 as elusive and is

apparently related to an unpredictability in proper protein folding during expression. In column 1 line 66 through column 2 line 59, various codon usage and context effects are described as problematic. In column 2 lines 53-59 the predictive value of statistical rules for preferred nucleotides adjacent to codons is described as relatively low. Hatfield et al go on to analyze codon pair usage frequencies wherein optimization of codon pair usage is then derived for determining polynucleotides which encode a protein or polypeptide in order to achieve an active polypeptide when made via a host cell culture such as described herein. This process, however, is complex and requires very specific host cell and polypeptide correspondence in order to perform the analysis to then make a useful and active protein. It is noted that the instant disclosure lacks any codon pair frequency analysis description for even a single host cell type. The Hatfield et al disclosure is a single procedural description which still lacks indication of how someone of skill in the art would test for appropriate antigenicity on which to base the codon usage analysis as disclosed therein. Thus, there would be no predictability as to what to direct a codon pair usage determination to as set forth in Hatfield et al. for the making of an active polypeptide. It is also pointed out that Hatfield et al. is a single disclosure and as such is not a well known practice for enabling the instant invention, and thus not available to applicant on this basis. Another disclosure of unpredictability in the art of codon usage is that of Nagata et al. (BBRC 261: 445-451 (1999)) wherein obstacles are summarized for the expression of genes in host mammalian cells on page 445, first paragraph after the abstract. Nagata et al. further describes an indication that codon study to clarify codon usage as related to polypeptide expression is known on page 445, second column lines 31-34. Nagata et al. was published years after issuance of the above cited Hatfield et al patent, and additionally documents the Hatfield disclosure as not being well known. Applicants cannot rely on a procedure in Hatfield et al as well known to assist in enabling the claimed invention.

The myriad of possible testing for active polypeptides reasonably would require undue experimentation itself. Normally in the art, a specific test would be required for polypeptide activity assessment even if cultured as described. Such a test is not apparent for assessment of operative vs inoperative polynucleotides and host cells for preparation of a useful fusion polypeptide comprising the two proteins or unspecified portions thereof.

This, in summary, the above described unpredictability for polynucleotide testing, or even what test to perform as well as host cell selection with corresponding codon, codon pair and/or codon context practice is supported by the number into enormous possibilities. No instant guidance to reasonable narrow the required experimentation leads to a determination of undue experimentation being required for both polynucleotide selection, and host cell selection that would result in an active and therefor useful fusion protein of an influenza protein and an unnamed stress protein or variant thereof.

(2) – the amount or direction presented-

None other than the above described general knowledge in the art, which still leaves undue experimentation for enabling the instant invention.

(3)- the presence or absence of working examples-

Specific fusion proteins, such as pET65MP/NP-B, pET65MP/NP-D are disclosed. Claims limited to these would be enabled. Specific influenza antigens named in the specification (and the claims) include nucleoprotein, neuraminidase, M1, M2, PB1, PB2 or PA, however, specific antigenic portions of those proteins are not specifically disclosed. No specific sequences of these proteins are disclosed. Specific stress proteins disclosed in the specification (and claims 92-94) include hsp65, hsp71, Hsp100-200, hsp90, LON, Hsp70, hsp60, TF55, Hsp40, FKBP, cyclophillin, Hsp20-30, ClpP, GrpE, Hsp10, ubiquitin, calnexin, or protein disulfide isomerase. Specific portions of these proteins which are useful in the fusion proteins are not disclosed in the specification. The specification does not provide any specific sequences for any of the stress proteins such that one of skill in the art would be able to make any of the stress proteins or fragments thereof. These proteins are disclosed only by name, without any other means to determine what the sequences should be.

(4)- the nature of the invention-

The invention is complex as there is no guidance as to which polypeptides, out of myriads possible to test for ability to generate a specific immune response once prepared. Even testing of polypeptide activity is generally a detailed process.

(5)- the state of the prior art-

Although many polypeptides have been cloned and expressed in culture, the Hatfield et al. summary indicates that the cultural expression of an active polypeptide is elusive and subject to many complex factors.

(6)- the relative skill of those in the art-

The cultural expression of polynucleotides in vectors in host cells to make a polypeptide is generally performed by graduate level or even more highly skilled individuals and is subject to numerous complex considerations for successful results. Even with this skill level, an unsuccessful result is frequently obtained, as noted above by Hatfield et al.

(7)- the predictability or unpredictability of the art-

The factors for making a useful and thus enabled polypeptide are elusive and unpredictable for a polypeptide wherein the polynucleotides which encode it for any host must be determined as described above.

(8)- the breadth of the claims-

The claims are directed to encompass a broad genus of unspecified fusion proteins. This is extremely broad regarding polynucleotides, vectors, and host cells that may be implemented in order to carry out the invention. As discussed above, the claim lacks any specificity as to what polynucleotides, vectors or host cells within this wide breadth of claim practice would be useable to result in the generation of an active polypeptide that can provoke the required response.

Thus, in conclusion, the above rejected claims lack enablement due to undue experimentation required to produce the claimed polypeptides, and the undue experimentation required to practice the claimed methods.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (571) 272 0723

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, PhD can be reached on (571) 272 0718. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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MARY K. ZEMAN
PRIMARY EXAMINER

AU 1631
3/6/06